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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 38/21</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/31213</b> <b>(43) International Publication Date:</b> 23 November 1995 (23.11.95)
<b>(21) International Application Number:</b> PCT/EP95/01825 <b>(22) International Filing Date:</b> 15 May 1995 (15.05.95)  <b>(30) Priority Data:</b> RM94A000300 16 May 1994 (16.05.94) IT  <b>(71) Applicant (for all designated States except US):</b> APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. [NL/NL]; 6 John B. Gorsiraweg, Curaçao (AN).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SAMARITANI, Fabrizio [IT/IT]; Via Luigi Chiala, 130, I-00139 Rome (IT). NA-TALE, Patrizia [IT/IT]; Via Tirso, 80, I-00198 Rome (IT).  <b>(74) Agent:</b> VANNINI, Mario; Istituto Farmacologico Sersono S.p.A., Via Casilina, 125, I-00176 Rome (IT).		<b>(81) Designated States:</b> AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> IFN- $\beta$ LIQUID FORMULATIONS  <b>(57) Abstract</b>  Interferon-beta liquid formulations stabilized with a polyol, a non-reducing sugar or an amino acid. In particular, the formulations are stabilized with a polyol, such as mannitol. The formulations, preferably, furthermore comprise a buffer, such as acetate buffer, at a pH comprised between 3.0 and 4.0 and human albumin at a minimum quantity. The interferon-beta is preferably recombinant.		

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IFN- $\beta$  LIQUID FORMULATIONS

The present invention relates to liquid formulations of interferon-beta (IFN- $\beta$ ) stabilised with a polyol, a non-reducing sugar or an amino acid. In particular, it relates to liquid formulations containing mannitol, human albumin and acetate buffer.

Interferons (alpha, beta, gamma) are glycoproteins produced in the cells of vertebrates following induction. The most traditional inducers are virus, but also other microbial agents, other natural substances and synthetic compounds have the same behaviour.

Interferon- $\beta$  is induced in human fibroblasts, has anti-viral activity, but in the therapy of some tumoral forms other activities can be exploited together with the anti-viral, such as the anti-proliferative cellular activity and immunoregulatory activity.

Production from culture of human fibroblasts, and specifically from recombinant DNA techniques, now allows to obtain industrial quantities of interferon-beta.

It is known that proteins in the purified form are especially susceptible to degradation, even due to the normal activity of atmospheric agents. This peculiarity becomes even more evident for proteins produced according to recombinant DNA techniques.

As a direct consequence of the fact that highly purified proteins are easily subject to denaturization, it becomes desirable to obtain stable formulations which ensure the longest possible life-cycle to the product.

Stabilisation of formulations containing highly purified proteins may be carried out by the addition of one or more excipients which inhibit or delay degradation of the active principle.

Pharmaceutical compositions containing interferon-beta are well known. EP Patent application 89 245 (INTER-YEDA Ltd) describes a lyophilised composition of interferon-beta containing mannitol, human albumin and polyvinylpyrrolidone, the latter as stabilising agent. Also known are pharmaceutical liquid compositions containing other interferons.

International Patent Application WO 89/04177 (GENENTECH - Priority 03/11/87) describes liquid pharmaceutical formulations of gamma-

interferon comprising a buffer which maintains the pH within the range of 4.0-6.0, a polyhydroxylate sugar as stabiliser and a non-ionic detergent.

EP Patent Application 270 799 describes IFN- $\beta$  pharmaceutical compositions in liquid form or lyophilized, which comprise, as  
5 solubilizer/stabilizer, one or more non-ionic polymeric detergents.

It is highly desirable to obtain such liquid formulations in order to avoid the reconstitution of lyophilised preparations and thus to permit ease of use.

It has now surprisingly been found that liquid pharmaceutical  
10 formulations comprising interferon-beta stabilised with a polyol, a non-reducing sugar or an amino acid in an appropriate buffer result particularly stable and maintain biological activity for a long period of time.

The main object of the present invention is to provide a liquid pharmaceutical formulation comprising interferon-beta and a polyol, a non-  
15 reducing sugar or an amino acid, as stabiliser.

Preferably the stabiliser is selected from mannitol, saccharose and glycine; more preferably, the stabiliser is mannitol.

Preferably the liquid pharmaceutical formulation comprises a buffer with a pH between 3 and 4; more preferably, acetate buffer.

Another object of this invention is to provide a process for the  
20 preparation of such liquid pharmaceutical formulation comprising the stage of dilution of IFN- $\beta$  with a solution of the excipients.

Yet another object of the present invention is to provide a presentation form of the liquid pharmaceutical formulation comprising the  
25 previously mentioned formulation, hermetically sealed under sterile conditions in a container suitable for storage prior to use.

To study the stability of liquid formulations of IFN- $\beta$ , various formulations were prepared diluting bulk IFN- $\beta$  in different buffers at varying pH, then storing the samples at different temperatures and carrying  
30 out assays with the immunological test at set intervals of time. Once the buffer solution and the preferred pH, with which the greater stability is obtained, have been selected, then the stabilised formulations of the invention are prepared by diluting the interferon bulk solution with the buffer solution containing also the excipients. Stability of the various  
35 formulations was determined by measuring the residual activity of IFN- $\beta$  at

fixed intervals of time, after storage of the solution at the temperatures of 50°C, 37°C, and 25°C.

To determine such activity, samples were assayed under immunological and biological tests.

5       The immunological test was carried out by using the TORAY kit (Human IFN-Beta ELISA Kit, TORAY INDUSTRIES, Inc.), following the methodology reported in the enclosed instructions.

10       The biological dosage was performed as described by Armstrong J.A. (1981), Cytopathic effect inhibition assay for Interferon, in *Methods in Enzymology* 73 381-387. This test permits the measuring of IFN- $\beta$  activity by exploiting its anti-viral capacity.

Measure of activity is expressed in International Units per millilitre of solution (IU/ml) or in Mega International Units per millilitre of solution (MIU/ml). (1 MIU/ml = 1,000,000 IU/ml).

15       An International Unit is calculated as described in the Research Reference Reagent Note No. 35, published by the National Institute of Health, Bethesda, Maryland, in relation to the HuIFN-beta NIH Reference Reagent Gb 23-902-531 used as standard.

20       The measurement is reported here as percentage of residual activity of the sample of Interferon-beta in the various formulations, taking activity of the sample at time zero as equal to 100%.

Dosages were carried out in duplicate.

25       To assess the effect of the pH on stability of the active ingredient, different formulations of recombinant IFN- $\beta$  were prepared containing 0.6 and 1 MIU/ml with various buffer solutions, i.e. acetate buffer, citrate buffer, ascorbate buffer, succinate buffer.

30       The formulations containing recombinant IFN- $\beta$  with the buffer solutions were prepared and stored at temperatures of 50°C, 37°C and 25°C, then assayed under the immunological test at set time intervals. The formulations were prepared in such a way as to have a pH between 3.0 and 4.0 and between 5.0 and 6.0, all with buffer at a concentration of 0.01 M.

Tables 1, 2 and 3 report results of tests carried out at set intervals of time, from 1 to 42 days, at the various temperatures.

35       Data contained in the above-mentioned tables indicate that the formulations with a pH between 5.0 and 6.0 show an immediate loss of

titre. Formulations with pH between 3.0 and 4.0 show, however, a high stability, especially in the presence of acetate buffer.

To assess the effect of excipients on the stability of the active principle, different formulations were prepared containing 1 MIU/ml of  
5 recombinant IFN- $\beta$ , using various excipients such as mannitol, saccharose or an amino acid such as glycine, and human albumin already partially contained in the interferon-beta bulk solution.

Quantities of mannitol, saccharose or glycine used were such as to obtain isotonic solutions of IFN- $\beta$ .

10 Stability studies on these formulations were carried out by maintaining samples at 50°C, 37°C, 25°C and 4°C, and measuring residual activity at the times reported in tables 4 and 5.

Data reported in tables 4 and 5 show that degradation in the formulations containing a polyol like mannitol is much lower in respect to  
15 those formulations containing saccharose or glycine.

The formulation selected for a deeper study was the one containing mannitol in 0.01 M acetate buffer at pH 3.5, which was subjected to further tests for evaluation of the effect on stability of the ionic force and the albumin.

20 Solutions of IFN- $\beta$  in 0.01 M acetate buffer at pH 3.5, were prepared at different values of osmolality: 150, 300 and 400, and with different dielectric constants, with 5, 10, and 20 % propylene glycol, and samples were then stored and assayed at 50°C, 37°C and 25°C. The study shows that increase of osmolality and the propylene glycol content decreased  
25 stability of the liquid formulations of IFN- $\beta$ .

Since bulk IFN- $\beta$  contains albumin, it was decided to proceed to a study for evaluation of the effect of albumin on the stability of interferon- $\beta$  liquid formulations. Samples containing IFN- $\beta$  (1 MIU/ml) and the acetate buffer solution at pH 3.5 were added to 1, 3, 6, and 9 mg/ml of human  
30 albumin and tested at temperatures of 50°C, 37°C and 25°C.

Results show that with the increase of albumin the stability of the samples decreased. The albumin content per sample was fixed in such a way as to have the minimum quantity compatible with that contained in the various bulks: in a formulation containing 1 MIU/ml of IFN- $\beta$ , a uniform  
35 content of 0.5 mg/ml albumin is maintained.

**EXAMPLES of PHARMACEUTICAL PRODUCTION**

Materials : mannitol (Merck); human albumin (Boehring); 0.01 M acetate buffer (Merck); NaOH 1M (Merck).

DIN 2R glass bottles (glass type I borosilicate glass) with stoppers of Pharmagummi rubber, butylic mixture, and aluminium ring, were used as containers.

***Example of preparation of r-IFN- $\beta$  solution*****A) SOLUTION AT 1 MIU/ML**

For the preparation of a batch of 1 Lt. of finished product, the following quantities are used:

r-interferon-beta	1000 MIU
Mannitol	54.6 g
Human albumin	0.5 g-P
0.01 M pH 3.5 acetate buffer	q.s. to 1 Lt.

P = amount of human albumin present in bulk interferon.

**B) SOLUTION AT 12 MIU/ML**

For the preparation of a batch of 1 Lt. of finished product, the following quantities are used:

r-interferon-beta	12000 MIU
Mannitol	54.6 g
Human albumin	4.0 g-P
0.01 M pH 3.5 acetate buffer	q.s. to 1 Lt.

P = amount of human albumin present in bulk interferon.

**C) SOLUTION AT 24 MIU/ML**

For the preparation of a batch of 1 Lt. of finished product, the following quantities are used:

r-interferon-beta	24000 MIU
Mannitol	54.6 g
Human albumin	8.0 g-P
0.01 M pH 3.5 acetate buffer	q.s. to 1 Lt.

P = amount of human albumin present in bulk interferon.

**Method of Preparation**

The required quantity of mannitol and human albumin (taking into account the quantity of albumin present in the bulk) is dissolved in approximately 500 g of 0.01 M pH 3.5 acetate buffer. The pH is checked



and, if necessary, adjusted to the value of  $3.5 \pm 0.2$  with diluted (1:2) acetic acid or with 1 M NaOH.

The solution is brought to the final weight of 1 Kg with 0.01 M pH 3.5 acetate buffer.

5        The required quantity of r-interferon beta is weighed in a beaker and brought to the final weight of 500 g with the solution of excipients.

10        In another beaker 500 g of solution of excipients is weighed. The 500 g of solution containing interferon-beta is filtered on a sterile membrane of  $0.22 \mu\text{m}$  (DURAPORE) at a pressure not exceeding 1.5 atm. The sterile solution is collected in a glass erlenmeyer flask. Immediately afterwards the 500 g of excipient solution is filtered on the same membrane at a pressure of 1.5 atm and collected in the same erlenmeyer flask. The solution obtained is slowly mixed.

**TABLE 1**  
**r-INTERFERON- $\beta$**

**LIQUID FORMULATION : 1 MIU/BOTTLE**  
**RESULTS IMMUNOLOGICAL DOSAGE :**  
**CONCENTRATION (%)**  
**STABILITY IN 0.01 M CITRATE BUFFER AT**  
**DIFFERENT pH VALUES**

50°C								37°C		25°C	
	T = 0	1 D	30 D	19 D	30 D	12 D	19 D				
	IFN/3	100 (890600 IU/ML)	73.0	8.6	88.5	69.9	100	97.5			
	IFN/4	100 (820900 IU/ML)	20.1	1.0	68.7	36.6	100	62.8			
	IFN/5	100 (532100 IU/ML)	ND					43.6			
	IFN/6	100 (179500 IU/ML)	ND								

D = day(s)

ND = non-determinable

IFN/3 = formulation in citrate buffer pH 3.0

IFN/4 = formulation in citrate buffer pH 4.0

IFN/5 = formulation in citrate buffer pH 5.0

IFN/6 = formulation in citrate buffer pH 6.0

**TABLE 2**  
**r-INTERFERON- $\beta$**

**LIQUID FORMULATION : 0.6 MIU/BOTTLE**  
**RESULTS IMMUNOLOGICAL DOSAGE :**  
**CONCENTRATION (%)**  
**STABILITY IN 0.01 M ACETATE BUFFER AT DIFFERENT**  
**pH VALUES**

	50°C			37°C		25°C	
	T = 0	1 D	30 D	19 D	30 D	7 D	19 D
<b>IFN/3</b>	100 (549425 IU/ML)	72.6	48.3	97.5	100	100	100
<b>IFN/4</b>	100 (459600 IU/ML)	77.6	30.3	91.9	92.2		100
<b>IFN/5</b>	100 (52275 IU/ML)	45.0					
<b>IFN/6</b>	100 (25425 IU/ML)	57.2					

D = day(s)

IFN/3 = formulation in acetate buffer pH 3.0

IFN/4 = formulation in acetate buffer pH 4.0

IFN/5 = formulation in acetate buffer pH 5.0

IFN/6 = formulation in acetate buffer pH 6.0

**TABLE 3**  
**r-INTERFERON- $\beta$**

**LIQUID FORMULATION : 1 MIU/BOTTLE**

**RESULTS IMMUNOLOGICAL DOSAGE : CONCENTRATION (%)**

**STABILITY IN 0.01 M ASCORBATE & SUCCINATE BUFFER AT pH 3.00 & 4.00**

		50°C				37°C				25°C			
		T = 0	7 D	14 D	21 D	7 D	42 D	7 D	42 D	7 D	14 D	42 D	42 D
IFN/3/ASC	100	(1068400 IU/ML)	ND				32.4			76.5	10.5		
	100	(1025000 IU/ML)	ND				15.6			80.6			
IFN/3/SUC	100	(980200 IU/ML)	62.9	54.8	22.1	92.7	87.8	96.0	62.5	97.2			
	100	(957600 IU/ML)	62.8	43.8	22.7	88.5	14.3		78.7	84.7			

D = days

ND = non-determinable

IFN/3/ASC = formulation in ascorbic buffer pH 3.0; IFN/4/ASC = formulation in ascorbic buffer pH 4.0

IFN/3/SUC = formulation in succinate buffer pH 3.0; IFN/4/SUC = formulation in succinate buffer pH 4.0

**TABLE 4**  
**r-INTERFERON- $\beta$**

**LIQUID FORMULATION : 1 MIU/BOTTLE**

**RESULTS BIOLOGICAL DOSAGE : CONCENTRATION (%)**

**STABILITY IN 0.01 M ACETATE BUFFER AT pH 3.5 with DIFFERENT EXCIPIENTS**

	T = 0	50°C	37°C	25°C			
		49 D	49 D	3 M	3 M	6 M	9 M
<b>ACE/SAC /3.5</b>	100 (970000 IU/ML)	25.8	100	85.6	100	100	
<b>ACE/MAN/3.5</b>	100 (1150000 IU/ML)	67.8	100	90.4	91.3	100	85.2
<b>ACE/GLY /3.5</b>	100 (1200000 IU/ML)	49.2	100	75.8	90.0	98.3	

D = days

M = months

ACE/ SAC /3.5 = formulation in acetate buffer pH 3.5 + saccharose

ACE/MAN/3.5 = formulation in acetate buffer pH 3.5 + mannitol

ACE/ GLY /3.5 = formulation in acetate buffer pH 3.5 + glycine

**TABLE 5**  
**r-INTERFERON-β**

**LIQUID FORMULATION : 1 MIU/BOTTLE**  
**RESULTS IMMUNOLOGICAL DOSAGE : CONCENTRATION (%)**  
**STABILITY USING DIFFERENT EXCIPIENTS IN 0.01 M ACETATE BUFFER AT pH 3.5**

		50°C				37°C				25°C				4°C			
		T = 0		7 D	14 D	49 D	14 D	49 D	3 M	6 M	9 M	3 M	6 M	9 M	3 M	6 M	9 M
ACE/SAC /3.5	100	(1120000 IU/ML)		78.6	62.5	10.3	99.1	96.4	67.1	97.2		100	100		100	100	
ACE/MAN/3.5	100	(1070000 IU/ML)		90.6	74.8	60.3		100	100	100	100	100	100	100	100	100	100
ACE/GLY /3.5	100	(1220000 IU/ML)		77.0	47.5	19.4	100	91.0	93.9	96.9		87.7	100				

D = days

M = months

ACE/ SAC /3.5

= formulation in acetate buffer pH 3.5 + saccharose

ACE/MAN/3.5

= formulation in acetate buffer pH 3.5 + mannitol

ACE/ GLY /3.5

= formulation in acetate buffer pH 3.5 + glycine

CLAIMS

1. A liquid pharmaceutical formulation comprising interferon-beta and a polyol, a non-reducing sugar or an amino acid as stabilising agent.
- 5 2. A liquid pharmaceutical formulation according to claim 1, in which the stabilising agent is selected from: mannitol, saccharose and glycine.
3. A liquid pharmaceutical formulation according to claim 2, in which the  
10 stabilising agent is mannitol.
4. A liquid pharmaceutical formulation according to any of the claims from 1 to 3, in which interferon-beta is recombinant.
- 15 5. A liquid pharmaceutical formulation according to any of the claims from 1 to 4, in which interferon-beta is in a quantity between 0.6 and 1 MIU/ml.
- 20 6. A liquid pharmaceutical formulation according to any of the claims from 1 to 5, which comprises, furthermore, a buffer solution capable of maintaining the pH of the liquid formulation at a value between 3.0 and 4.0.
- 25 7. A liquid pharmaceutical formulation according to claim 6, in which the buffer solution is acetate buffer.
8. A liquid pharmaceutical formulation according to claim 6 or 7, in which the buffer solution has a concentration of 0.01 M.
- 30 9. A liquid pharmaceutical formulation according to any of the claims from 1 to 8, which also comprises human albumin.
10. A liquid pharmaceutical formulation according to any of the claims from 1 to 9, comprising 1 MIU/ml of interferon-beta, 54.6 mg/ml of

mannitol, 0.5 mg/ml of albumin in a solution of 0.01 M acetate buffer at pH 3.5.

- 5 11. Process for the preparation of a liquid pharmaceutical formulation according to any of the claims from 1 to 10, comprising the dilution of interferon-beta with a solution of excipients.
- 10 12. Presentation forms of the liquid pharmaceutical formulation according to any of the claims from 1 to 10, hermetically sealed in sterile conditions in a container appropriate for storage prior to use.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/01825

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 38/21

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, WPI, WPIL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5183746 (SHAKED ET AL), 2 February 1993 (02.02.93), column 13, line 11 - line 18, column 14, lines 22,23,29, column 15, line 19 --	1-12
X	US, A, 4465622 (NOBUHARA ET AL), 14 August 1984 (14.08.84), column 3, line 25 - line 36; column 5, line 16 - line 20, claims 5,16-19 --	1-12
X	WO, A1, 8902750 (CETUS CORPORATION), 6 April 1989 (06.04.89), claims 1-2 --	1-12

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Date of the actual completion of the international search

22 Sept 1995

Date of mailing of the international search report

31.10.95

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/01825

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>Dialog Information Services, file 351, WPIL, Dialog accession no. 003925794, WPI accession no. 84-071338/12, TORAY IND INC: "Stabilising beta-interferon having no sugar chain by adding polyol, e.g. ethylene glycol, glycerine or sugar, esp. oligo saccharide", JP 59025333, A, 840209, 8412 (Basic)</p> <p>-- -----</p>	1-12

# INTERNATIONAL SEARCH REPORT

Information on patent family members

28/08/95

International application No.

PCT/EP 95/01825

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5183746	02/02/93	AU-A- 2535188	18/04/89
		WO-A- 8902750	06/04/89
		AT-T- 111744	15/10/94
		AU-B- 659127	11/05/95
		AU-A- 1063392	19/03/92
		AU-A- 8019187	28/04/88
		CA-A- 1294215	14/01/92
		DE-D,T- 3750574	02/02/95
		EP-A,B- 0270799	15/06/88
		JP-A- 63179833	23/07/88
		NO-B,C- 175704	15/08/94
US-A- 4465622	14/08/84	CA-A- 1185178	09/04/85
		DE-A,C,C 3223087	17/02/83
		FR-A,B- 2510409	04/02/83
		GB-A,B- 2111061	29/06/83
		JP-C- 1444652	08/06/88
		JP-A- 58021691	08/02/83
WO-A1- 8902750	06/04/89	JP-B- 62054440	14/11/87
		AU-A- 2535188	18/04/89
		US-A- 5183746	02/02/93